

REMARKS

Claims 1, 2, 5-14, 16 and 17 are pending in the application. Claims 3, 4 and 15 are canceled. Claims 1, 2, 7, 8, 9, 11, 12, 16 and 17 are amended. Applicants reserve the right to pursue any withdrawn or canceled subject matter in one or more continuation or divisional applications.

Rejections under 35 U.S.C. §112

The Examiner has rejected claim 1 under 35 U.S.C. §112 second paragraph as indefinite because it is allegedly unclear to whom the compound is being administered. The claims have been amended to recite that the compound is administered to “a human patient in need thereof” to overcome this rejection.

The Examiner has also rejected claims 1, 11 and 16 for the recitation “optionally substituted.” It would be clear to one skilled in the art that the residues of the amino acid, as described in the specification on page 7, line 1-3, can be optionally substituted.

The Examiner has also rejected claim 1 stating that it is not clear whether Ile represents a substitution on another amino acid or a different substitution for R₁. The claims have been amended to clarify that residue R₁ is, alternatively, a residue that is “derived from Ile.”

The Examiner’s suggestion on wording of claim 11 has been incorporated.

The Examiner has objected to the recitation of “N,N-diethyl-isoleucyl-isoleucyl-prolineamide” in claims 14 and 17 as not having sufficient basis in claim 11 because claim 11 fails to define R₁ as Ile. Please note that the claim originally stated that R₁ is alternatively Ile, and has been amended to clarify that R₁ can be a residue derived from the amino acid Ile.

Prior Art Rejections under 35 U.S.C. §§ 102 and 103

The Examiner has rejected claims 1, 3-7 and 9 under 35 U.S.C. §102(b) and claims 1-14, 16 and 17 under 35 U.S.C. §103(a) over Masuyama, et al. (US 6,410,685).

The '685 patent is directed to the treatment of stress using certain tripeptides, namely either Ile-Pro-Pro or Val-Pro-Pro. Amended claims 1, 2, 5-10 and 16 are directed to the treatment of a neurodegenerative disease by administration to a patient in need thereof of certain proline-derivative tripeptides, defined in the amended claims and amended claims 11-14 and 17 recite pharmaceutical compositions of these compounds. The compounds recited in the amended claims are not disclosed in the '685 patent. The '685 patent discloses only certain tripeptides that are either Ile-Pro-Pro or Val-Pro-Pro. The amended claims recite proline derivatives with residues R₁ and R₂ that are a residue derived from Phe or Ile (R₁) and Gly or Ile (R₂). The amended claims do not include compounds that are described by the '685 patent.

These claims are also not rendered obvious by the disclosure of a different set of compounds in the '685 patent. The '685 patent focuses exclusively on two peptides that differ from those in the amended claims for the treatment of physiological stress. The '685 patent does not disclosure or suggest the use of any tripeptides for the treatment of neurodegenerative diseases. A skilled artisan would have no way to identify the compounds described in the amended claims for the treatment of neurodegenerative diseases based on a disclosure of *different* compounds for the treatment of a *different* condition. The utility of the compounds recited in the amended claims is apparent from the examples in the disclosure which show that the recited compounds have effect on neurological deficits *in vivo*, as described in Example 6. The disclosure of the '685 patent therefore does not suggest either the pharmaceutical compositions or methods of treatment of neurodegenerative diseases with the proline-derived compounds recited in the amended claims.

The Examiner has also rejected claims 1-8, 11-12 and 16 under 35 U.S.C. §102(b) and claims 1-14 and 16-17 under 35 U.S.C. §103(a) over Yoshimasa, et al. (JP 09169797).

The '797 application describes the use of certain peptides with protease activator activity. The abstract of the '797 patent describes peptides of formula I, namely Pro-A-B where A is Phe, Lys, Asn, Tyr or Thr; B is Pro or Trp (see abstract). In contrast, the amended claims recite proline derivatives with two other amino acid residues that are derived from Phe or Ile (R_1) and Gly or Ile (R_2). The amended claims do not include compounds that are described in the '797 application. As discussed above, there is no way to predict that the compounds of the amended claims could be effective for treatment of neurodegenerative diseases based on a disclosure of *different* compounds for the treatment of a different condition. The disclosure of the '797 application therefore neither teaches nor suggests either the compositions or methods of treatment of the amended claims.

Claims 1-8, 11-12 and 16 are rejected under 35 U.S.C. § 102(b) and claims 1-14, 16 and 17 under 35 U.S.C. §103(a) over Yoshimasa, et al. (JP 09040577).

The '577 application describes compositions of tripeptides that are Pro-A-B where A is phenylalanine, lysine, etc. and B is proline or tryptophan (see abstract). The Examiner specifically indicates tripeptides of formula I that are Pro-Phe-Pro and Pro-Phe-Pro-NH₂. As described above, the compounds recited in the amended claims are not described in the '577 application. The amended claims recite proline derivatives with R_1 and R_2 that are residues derived from Phe or Ile (R_1) and Gly or Ile (R_2). The '577 application therefore does not teach the compounds of the amended claims. As discussed above, the disclosure of *different* compounds for the treatment of different conditions also does not suggest either the methods or the pharmaceutical compositions of the amended claims, as a skilled artisan would have no guidance for the development of pharmaceutical compositions including compounds of the amended claims, and would have no way to predict that any tripeptide compound would be useful for the treatment of neurodegenerative diseases based on the '577 application.

The Examiner has also rejected claims 1, 3-9, 11 and 16 under 35 U.S.C. §102(b) and claims 1-14, 16 and 17 under 35 U.S.C. §103(a) over Hathaway (WO 92/13549).

The '549 publication generally describes hydrophobic peptides for the inhibition of cell proliferation. Although a large generic genus of peptides is described in the specification, no specific disclosure teaches the peptides covered in the amended claims, namely compounds in which R_1 is a residue derived from Phe or Ile and R_2 is a residue derived from Gly or Ile. The genus described in the '549 publication is compounds of the general formula $R-Xaa_1-(Xaa)_m-Xaa_c$, in which Xaa_1 and Xaa_m are independently Ala, Arg, Ile, Leu, Lys, nLeu, Phe, Pro, Thr, Tyr, Trp, Val and Xaa_c is Ala, Arg, Cys, Ile, Leu, Lys, nLeu, Phe, Pro, Thr, Tyr, Trp, Val or a derivative thereof, and m is 0-5. There are therefore several thousand variations of this genus. The specification provides no specific teaching of the proline-derivatives recited in the amended claims.

The specification also does not suggest the compounds recited in the amended claims, as the specific disclosure is directed to peptides have carboxy-terminal amino acids that are aldehyde derivatives of Leu, Lys, nLeu, Phe or Tyr (page 11, lines 14-16) and the most preferred peptides are leucine derivatives (page 11, lines 19-20). The '549 publication also does not suggest that any tripeptides could be useful for the treatment of neurodegenerative diseases, let alone the tripeptides recited in the amended claims. The '549 publication teaches that certain tripeptides are allegedly useful for the inhibition of cell proliferation. This is taught as being particularly useful for the treatment of cancer, prostatic hypertrophy, arteriosclerosis, etc. It would have been counterintuitive for a skilled artisan to use any compounds that are taught to prevent cell proliferation when trying to treat neurodegenerative diseases, which are related to the *degeneration* of cells. The utility of the compounds of the amended claims is apparent from the disclosure in the present application. The '549 publication therefore, insofar as it teaches tripeptides for the use in any diseases, *teaches away* from the use of any of these peptides for the treatment of neurodegenerative disease. Therefore, the '549 publication does not suggest the use of the compounds recited in the amended claims in any compositions, nor does it suggest the use of any tripeptides, particularly not those recited in the amended claims, for the treatment of neurodegenerative diseases.

The Examiner also rejects claims 1, 3-8, 11 and 16 under 35 U.S.C. §102(b) and claims 1-14, 16 and 17 under 35 U.S.C. §103(a) over Maruyama et al. (EP 0445606). The '606 patent describes certain tripeptides that are allegedly angiotensin converting enzyme inhibitors that are generally of the formula: Leu-Xaa-Pro where Xaa is Gly, Ala, Val, Ile, Thr, Asp, Glu, Lys, Orn, Cys, Met, Phe, Tyr, Trp, His or a hydroxyproline residue or are Leu-Ser-Pro, Leu-Gln-Pro, Val-Ser-Pro, Leu-Leu-Pro, Leu-Asn-Pro, Phe-Leu-Pro, Leu-Ala-Ala, Val-Ala-Ala, Leu-Gln-Gln, Val-Ala-Tyr, Leu-Ala-Tyr, Leu-Ser-His, Ile-Arg-Ala, Leu-Arg-Pro. The amended claims recite proline-derived tripeptide compounds in which R₁ is a residue derived from Phe or Ile and R₂ is a residue derived from Gly or Ile. The '606 patent does not teach or suggest the compounds recited in the amended claims. Furthermore, the '606 patent does not teach or suggest the use of any tripeptides for the treatment of neurodegenerative diseases, and instead focuses on hypertension and other diseases related to the renin-angiotensin system. There is therefore no suggestion in the '606 patent of either the compositions or methods of treatment recited in the amended claims.

The Examiner has also rejected claims 1-14, 16 and 17 under 35 U.S.C. §103(a) over Hathaway or Masuyama in view of Yoshimasa et al. As none of the primary references render obvious the amended claims, and the secondary reference teaches neither the specific compounds, nor the methods of treatment of neurodegenerative diseases recited in the amended claims. It is requested that this rejection be withdrawn.

Double Patenting

The Examiner has provisionally rejected claims 1-10 and 16 under the judicially created doctrine of obviousness-type double patenting over claims 1-8 of copending Application No. 10/635,805. The Examiner has apparently equated the treatment of neurodegenerative diseases disclosed in the pending application with the treatment of postlesional diseases disclosed in the '805 application.

Contrary to the Examiner's assertion, these claims do not cover overlapping subject matter. A postlesional disease of toxic origin, as recited in the '805 application, is *not* the same as a neurodegenerative disease and *does not* encompass Alzheimer's disease or amnesia, as indicated by the Examiner. A postlesional disease of toxic origin is induced by exogenous toxins such as alcohol, drugs, heavy metals, etc. In support of this, Alzheimer's disease and postlesional diseases of toxic origin are differently classified by the World Health Organization. Alzheimer's is classified in block 30 of the International Statistical Classification of Diseases and Related Health Problems (see www.who.int/whosis/icd10/) while postlesional diseases of toxic origin (i.e. intoxication) are classified as 'injury' in block S. A skilled person therefore can clearly distinguish Alzheimer's disease from a postlesional disease of toxic origin.

The Examiner has also indicated that amnesia is considered a postlesional disease of traumatic origin. However, amnesia is not a specific disease, but instead is a *symptom* that can have its origin both in neurodegenerative diseases such as Alzheimer's disease or can be induced, for example, by administering drugs such as scopolamine, diazepam or barbitol. Amnesia is not associated with (necrotic) cell death so that its treatment does not require nerve regeneration, but instead it is a reversible cognitive impairment.

U.S.S.N 10/635,797
Amendment dated April 15, 2005
Reply to Office Action dated October 15, 2004

Applicants believe no further fees are due with this response, however if the Examiner determines that any fees are due, the Commissioner is hereby authorized to charge any additional fees associated with this response to Deposit Account No. 11-0980.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Madeline Johnston", with a stylized flourish at the end.

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